

synthesizing compounds corresponding to at least some of said virtual compounds; and robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

REMARKS

Claims 55, 56, 58-72, 74-87, and 99-102 are pending in the present application. Claim 55 has been amended to harmonize the language of the claim. No new matter is added and no change in scope is intended. Upon entry of the present amendment, claims 55, 56, 58-72, 74-87, and 99-102 will remain pending.

I. No New Matter is Added to the Claims

Claim 55 has been amended to further clarify that synthetic compounds corresponding to virtual compounds modulate the expression of a target nucleic acid sequence. Applicants previously requested that claim 55 be amended to specify real compounds corresponding to virtual compounds modulate the expression of a target nucleic acid sequence. The Advisory Action alleges the phrase "real compounds" may introduce new matter and present new issues for further consideration. Although Applicants do not concur, the claim has been amended to employ alternative language, and thereby, moot the rejection. The phrase "synthetic compounds corresponding to virtual compounds" is consistent with terminology used in other claims as filed. See, e.g., claims 3, 4, and 6.

II. The Claimed Inventions Are Not Obvious

Claims 55, 56, 58-72, 74-87, and 99-102 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combination of U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis patent"), Uhlmann *et al.*, *Chem. Rev.*, 1990, 90, 543-584 (hereinafter, the "Uhlmann reference") and U.S. Patent No. 5,639,603 (hereinafter, the "Dower patent") taken further in view of U.S. Patent No. 5,720,923 (hereinafter, the "Haff patent") or U.S. Patent No. 5,650,122 (hereinafter, the "Harris

patent”). Applicants traverse the rejection and respectfully request reconsideration because the subject matter of claims 55, 56, 58-72, 74-87, and 99-102 is neither disclosed nor suggested by the collective teachings of the cited references.

The Agrafiotis patent utilizes a synthesis protocol generator to identify **reagents** that should be mixed together (Col 6, ll. 29-35). The synthesis protocol generator thus identifies a combination of reagents, not a virtual compound, a virtual nucleobase sequence, or a virtual nucleotide as recited in Applicants’ claims. Mere instructions to add, for example, two reagents from a reagent repository together to synthesize a particular member of a directed diversity library does not constitute *in silico* evaluation as recited in Applicants’ claims. The identification of mixing sequences of reagents says little, if anything, about the structure of compounds that may be produced. Thus, contrary to the Office Action’s assertion, the Agrafiotis patent does not disclose *in silico* evaluation of compounds.

The Advisory Action appears to allege that Applicants have attempted to distinguish the Agrafiotis patent by characterizing it as synthesizing pieces of the product rather than the entire product. This is incorrect. Applicants assert that the Agrafiotis reference does not disclose *in silico* evaluation of compounds. Contrary to the Advisory Action’s assertion, Applicants’ “nailing two boards to build a house” analogy does not suggest that the Agrafiotis patent does not build a “house” (i.e. entire product). Rather, the analogy makes clear that instructions to nail two boards together say little, if anything, about what a house containing such boards **will look like**. In other words, the Agrafiotis patent does not disclose what the product made by mixing reagents according to a set of instructions **will look like**.

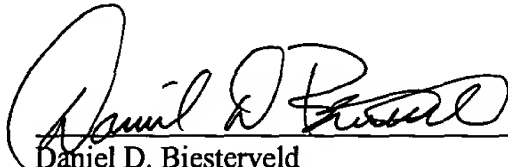
The remaining references do not supply that which is lacking from the Agrafiotis reference, nor does the Office Action contend that they do. In view of the foregoing, the claimed inventions are not obvious in view of the Agrafiotis patent and in view of the combination of other cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

III. Conclusion

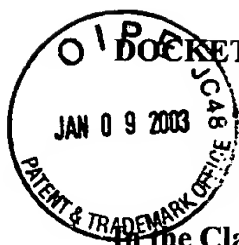
In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 557-5963 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Respectfully submitted,

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PATENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 55 has been amended as follows:

55. **(Amended Three Times)** A method comprising:

generating *in silico* virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, wherein synthetic compounds corresponding to said virtual compounds modulate the expression of a target nucleic acid sequence;

synthesizing compounds corresponding to at least some of said virtual compounds; and

robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.